REMARKS

Claims 77-101 are pending in this application. No claim amendments have been made.

Applicants note with appreciation the acceptance of the Request for Continued Examination and that the current action is non-final.

35 U.S.C. §101

Claims 77-101 stand rejected for allegedly lacking support by "either a specific and substantial utility or a well established utility." The rejection was maintained for reasons of record set forth in previous Office Actions dated March 21, 2003, March 18, 2005 and October 13, 2005.

In the Office Action dated May 19, 2006, the Examiner appears to object to the use of Graph 1 in arguments for utility. Graph 1 was submitted after the application filing date and was provided solely as corroboration (not assertion) of utility. While we continue to believe that Graph 1 can be used as corroboration of utility, for the purposes of this Response, we will ignore Graph 1 in the arguments used herein.

The specification asserts that the invention is useful as a way to screen for compounds (e.g. inverse agonists, agonists or partial agonists) that can be used as pharmaceutical agents among other things (see, for example, page 15, lines 14-17). The application discloses the sequence of a novel GPCR, hARE-2 (SEQ ID NO:20), and further discloses that this GPCR is expressed in a tissue restricted pattern in the substantia (see, for example, page 27, Table C). It was well established in the art at the time of the invention that GPCRs modulate the level of cAMP or IP3 in a cell and modulation of these second messenger molecules was known to affect neuronal viability. Further, it was well established in the art at the time of the invention that the viability of neurons in the substantia nigra is involved in the etiology of Parkinson's disease (PD). Therefore, the novel GPCR disclosed in the application can be used to screen for compounds that can increase the viability of neurons in the substantia nigra as a pharmaceutical agent for a disease such as PD. This well established utility is specific, substantial and credible.

We will now review in more detail the evidence from the specification and the art at the time of filing that supports the utility of the invention.

I. hARE-2 is a GPCR

There should be no question that the application discloses a novel sequence, hARE-2 (SEQ ID NO: 20), which belongs to the G-protein coupled receptor family of proteins (see, for example, page 17, line 18 and the sequence listing). The specification indicates that hARE-2 contains 53% homology to GPR27 (see, for example, page 8, line 4). In addition, as stated in earlier Responses, Figure 1 of priority provisional application US60/136,436 shows homology between hARE-2 and GPR27 over the entire length of hARE-2 (provided again herein as Appendix 1 for the Examiner's convenience). Applicants also note that this homology would have been apparent to one skilled in the art at the time of the invention as well because one could do a BLAST search to see the same thing. Further, as stated in earlier Responses, programs for predicting the location of the transmembrane domains of a GPCR based on sequence were available at least as early as the priority date of the application. One such method TMHMM (transmembrane hidden Markow model) predicts that hARE-2 contains seven transmembrane domains (provided again herein as Appendix 2 for the Examiner's convenience).

The sequence and TMHMM model also predicts that hARE-2 is a functional GPCR based on the presence of particular structural elements in the receptor. For example, as taught in the specification, TM-6 is characterized by a proline residue which is conserved in many GPCRs (see, for example, page 10, lines 9-12) and a tryptophan residue which was known in the art to be highly conserved (see Probst et al., (1992) DNA Cell Biol., 11:1-20, page 2, left column, lines 32-40 to right column, lines 1-5 and Figures 2 and 3, provided again herein as Appendix 3 for the Examiner's convenience). As can be seen in Appendix 2, hARE-2 contains a tryptophan residue in TM-6 at position 299 and a proline residue in TM-6 at position 301, consistent with the tryptophan and proline residues which are highly conserved in TM-6 of many GPCRs. It was also well known to the skilled artisan that functional GPCRs are characterized by a highly conserved arginine residue at the intracellular end of TM3, typically as part of a perfect or imperfect "DRY" motif (see Probst et al., page 12, left column, lines 30-34, Figures 2 and 3). hARE-2 contains the highly conserved arginine residue at the intracellular end of TM3 at amino acid position 121 (see Appendix 2). Therefore, based solely on the specification and what was known in the art at the time of the invention, the skilled artisan would predict that hARE-2 is a functional GPCR.

II. GPCRs are excellent drug targets

There should be no question that at the time of the invention GPCRs were known as an important family of proteins for drug discovery. Therefore, the skilled artisan would be

interested in screening a novel GPCR with a physiologically interesting pattern of tissue expression, like hARE-2, as a drug target.

As stated in the specification at page 3, lines 1-3 "GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, approximately 60% of all prescription pharmaceuticals have been developed."

III. hARE-2 is expressed in a tissue restricted manner in the substantia nigra.

There should be no question that the application discloses the expression of hARE-2 in the substantia nigra cells in the brain (see, for example, Table C on page 27). In addition, the expression of hARE-2 is disclosed as narrowly restricted to just the brain, and further, to only a few regions in the brain.

IV. GPCRs affect the level of cAMP or IP3 in a cell, which was known to affect neuronal viability.

The specification teaches that GPCRs affect the level of cAMP or IP3 in a cell (see, for example, page 3, line 21 to page 4, line 6, and page 12, line 2, to page 13, line 16). While the current Office Action argues that this is a general teaching, it nonetheless applies to hARE-2. Regarding the level of cAMP in a cell, as stated in previous Responses, it was known in the art at the time of the invention that that the viability of neurons in the substantia nigra is sensitive to the level of intracellular cAMP (Hulley et al., European Journal of Neurosciences (1995) 7:2431-2440 provided again herein as Appendix 4 for the Examiner's convenience). Regarding the level of IP3 in a cell, as stated in previous Responses, it was known in the art at the time of the invention that elevation of intracellular IP3 can lead to an elevation of intracellular calcium (Berridge, Nature (1993) 361:315-325, provided again herein as Appendix 4 for the Examiner's convenience). Further, it was known in the art that the viability of neurons in the substantia nigra is sensitive to the level of intracellular calcium (see Hirsch et al., J. Neural Transm Suppl (1997) 50:79-88, provided again herein as Appendix 4 for the Examiner's convenience). Therefore, one skilled in the art at the time of the invention would have expected that compounds acting on a GPCR expressed in neurons of the substantia nigra would affect neuronal viability, regardless of whether the receptor acted through cAMP or IP3.

Applicants submit that the specification provides several methods for screening a GPCR (see, for example, page 11, line 5, to page 15, line 12). Screening a library of compounds would naturally result in compounds which are agonists, antagonists, partial agonists, etc. These compounds can be easily tested in a substantia nigra neuronal viability assay (see, for

example, Hulley et al. in Appendix 4) to determine if an agonist or antagonist results in increased viability.

V. The viability of neurons in the substantia nigra is associated with Parkinson's disease.

There should be no question that at the time of the invention it was well known that the viability of neurons in the substantia nigra was associated with Parkinson's disease. As stated in previous Responses, it was known that Parkinson's disease is caused by a loss of neurons in the substantia nigra (see Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), McGraw-Hill (p. 504, lines 6-10, left column) and Blaszczyk (1998) Acta Neurobiol Exp (Wars) 58:79-93 (see Abstract lines 12-14), and Montastruc et al (1996) Drugs Aging vol. 169-184 (p. 170. line 47, left column to line 2 right column). Provided again herein as Appendix 5 for the Examiner's convenience.

Therefore, one skilled in the art, upon reading Applicants' specification, would have appreciated that modulating neuron viability in the substantia nigra would have been useful for treating a disease or disorder relating to degeneration of neurons of the substantia nigra, for example, Parkinson's disease. Thus those of skill in the art would have had no reason to doubt that hARE-2, which is disclosed as a GPCR which can affect the level of cAMP or IP3 in a cell, could be used in an assay to identify compounds that would be useful for modulating substantia nigra function to treat a disease or disorder of the substantia nigra, for example, Parkinson's disease.

Thus, a person of ordinary skill in the art, using only the teachings in the specification and what was known in the art, would have immediately appreciated that the claims directed to hARE-2 would have at least one well-established utility, because hARE-2 can be employed in a screening assay to identify, for example, compounds useful for treating a disease or disorder of the substantia nigra such as Parkinson's disease.

Regarding specific issues raised in the current Office Action, the Action alleges that Applicants have failed to provide a nexus between expression of the instant mRNA encoding hARE-2 protein and any diseases of the substantia nigra (see Action at page 3). Applicants respectfully submit that the nexus between hARE-2 and a disease of the substantia nigra such as Parkinson's disease would have been readily apparent to one skilled in the art based on the teachings of the specification and what was known in the art. As described above, the

specification teaches that hARE-2 is a GPCR and GPCRs affect the level of cAMP or IP3 in a cell. The art at the time of the invention teaches that modulation of the level of cAMP or IP3 in a cell can lead to modulation of neuronal viability. The specification teaches that hARE-2 is expressed in a tissue-restricted manner in the substantia nigra. Finally, it was well known in the art at the time of the invention that a decrease in viability of neurons in the substantia nigra is a hallmark of Parkinson's disease. The specification teaches that the GPCRs of the invention such as hARE-2 can be used to screen for compounds that can be used as pharmacological agents. Thus, using only what was disclosed in the specification and what was known in the art at the time of the invention, a nexus exists between hARE-2 and a disease of the substantia nigra such as Parkinson's disease.

The Office Action further alleges that significant further research would have been required to characterize the polypeptide of SEQ ID NO:20 to determine its biological activities (see Action at page 3). Applicants respectfully submit that SEQ ID NO:20 could be used to screen for compounds that affect substantia nigra neuronal viability, for example, as pharmaceutical agents to treat Parkinson's disease, using only the guidance in the specification and routine assays well known in the art. The specification provides guidance for how to perform screening assays (see, for example, the specification at page 11, line 5, to page 15, line 12) and such assays were well known in the art at the time of the invention. Compounds that are identified as affecting the hARE-2 receptor in a screening assay can then be easily tested using a routine substantia nigra neuronal viability assay to determine which compounds act to increase neuronal viability through the receptor (see, for example, Hulley et al. in Appendix 4).

The Office Action also alleges that it is unclear from the specification whether the hARE-2 protein functions as a GPCR (see Action at page 4). The Action alleges that structural similarity cannot accurately predict functional similarity (see Action at page 3). Applicants respectfully submit that in the case of GPCRs several structural features of these receptors were known at the time of the invention to indicate functional activity of the receptor. Upon seeing that a receptor contained these well known structural features, one skilled in the art would predict that the receptor is functional. These structural features are so highly correlated with function that no other experiment would be needed to proceed with using the receptor in a screening assay. However, if one wanted to corroborate that the receptor was functional, a routine assay such as a cAMP or IP3 assay could be used. These assays are taught in the specification (see, for example, page 12, line 2, to page 13. line 16) and were well known and routine in the art at the time of the invention.

The Office Action alleges at page 4 that it would have taken significant research to determine the role of hARE-2 in the substantia nigra and the role of hARE-2 in a disease such as Parkinson's disease and that only once these roles were determined could the receptor be used to screen for compounds. Applicants respectfully submit that for one skilled in the art at the time of the invention, sufficient linkage between the hARE-2 GPCR and Parkinson's disease was disclosed such that one would want to screen the receptor without delay. As described above, it was disclosed in the specification and known at the time of the invention that GPCRs are easily screened and are excellent drug targets. It was also known that GPCRs affect second messenger molecules that are known to affect neuronal viability. Given that the specification teaches that hARE-2 is specifically expressed in the substantia nigra, one skilled in the art would have sufficient information to begin screening the receptor even if the complete role of the receptor in Parkinson's disease was not yet known. In practice, the pace of drug discovery would be significantly slowed if one needed to wait until the complete role of a protein in a disease were known before one could begin screening for drugs. Indeed, several compounds are in clinical use today where the complete role of the compound or its target protein in the disease indication is not known.

Further, the Office Action alleges that hARE-2 belongs to a family of proteins, GTP-binding proteins, which are known to have a diversity of biochemical functions and be involved in a wide range of regulatory pathways such that assignment to this family does not support an inference of utility because the members are not known to share a common utility (see Action at pages 7-9). Applicant's respectfully submit that hARE-2 is not disclosed solely as a GPCR, but as a GPCR with a tissue-restricted pattern of expression in the substantia nigra. Not every GPCR could be considered as a drug target for Parkinson's disease, indeed, only a very small subset of GPCRs would fit this profile. The specification clearly shows that hARE-2 is one of a very small number of GPCRs that is a drug target for Parkinson's disease. This utility is specific, substantial and credible.

The Utility Standard

Applicants respectfully submit that the utility of the invention discussed herein meets the standard for utility set by the Office. According to MPEP § 2107.02, the Office must presume the utility set forth by Applicants is sufficient absent evidence of a reason to suspect otherwise. The MPEP states:

> Langer and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. See In re Langer, 503 F.2d at 1391, 183 USPQ at 297; In re Malachowski, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

The burden is upon the Office to provide evidence showing a reason to question Applicants' statements of utility. MPEP § 2107.02 continues to provide guidance in stating:

> in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. * * * This means that if the applicant has presented facts that support the countervailing facts and reasoning used in asserting a utility, Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility. In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false).

Thus, to establish lack of utility, the Office must provide evidence to contravene Applicants' statement of utility such that it is more likely than not that Applicants' assertion is false.

Applicants note that a well-established utility must also be specific, substantial and credible. As stated in previous Responses, the well established utility outlined above is specific, substantial and credible.

The Utility is Specific

Applicants respectfully submit that the utility is specific. Each of the claims is directed specifically to hARE-2 and not to GPCRs generally. The specification indicates that the localized expression data is used to determine where the receptor is expressed, and accordingly is associated with a functionality. In this case, expression was found in the substantia nigra--an area of the brain known to be correlated to motor function and motor impairment disorders. This knowledge coupled with the knowledge that modulation of hARE-2 (e.g., by a ligand identified through a screening assay that employs hARE-2) can lead to a modulation of cAMP or IP3 specifically in the substantia nigra, would lead those of ordinary skill in the art to recognize the identified ligand can be used specifically to treat a disease or disorder of the substantia nigra such as Parkinson's disease. Thus, the utility is specific as contemplated by 35 U.S.C. § 101.

The Utility is Substantial

The specification does not blindly recite the use of hARE-2 for treating an unknown disease or disorder, rather, the specification is clear that hARE-2 can be used to treat diseases and disorders associated with the substantia nigra, such as motor impairment diseases and disorders. The treatment of motor impairment disorders and, especially Parkinson's disease, is clearly a real world use. In this regard, Applicants note that the Revised Interim Utility Guidelines Training Material (herein after "Training Material") states that "an assay method for identifying compounds that themselves have a `substantial utility' define a `real world' context of use." See page 6 of the Training Material. In the present case, the compounds identified in an assay employing hARE-2 have substantial utility themselves because, as disclosed by Applicants, these compounds can be administered to treat a disease or disorder of the substantia nigra, such as Parkinson's disease. Thus, the use of hARE-2 in an assay to identify compounds thereof for treating disorders of the substantia nigra also would have a "real world" use. Thus, Applicants have disclosed a substantial, real world use as contemplated by 35 U.S.C. § 101.

The Utility is Credible

As mentioned above, it is the Office's burden to provide evidence tending to show that the utility is not credible. The Action offers no factual evidence to contravene Applicants' assertion of utility. Absent any factual evidence from the Office that would lead one to question the credibility of the utility, the Office must recognize the asserted or well established utility.

Applicants respectfully submit that all the requirements of 35 U.S.C. § 101 have been satisfied. Those of skill in the art would have had no reason to question the use of the GPCR, hARE-2, which is expressed in the substantia nigra, to screen for compounds that could be administered to a patient to treat a disease or disorder of the substantia nigra, such as Parkinson's disease.

Based on the evidence provided above, using only the teachings in the specification and what was well established in the art at the time of filing, we provide a well established, specific, substantial and credible utility for the claimed hARE-2 sequence. As outlined above, we show in the application that hARE-2 is a GPCR and that it is specifically expressed in the substantia nigra. In addition, the specification teaches that GPCRs affect the level of cAMP or IP3. It was well established in the art at the time of filing that GPCRs are excellent targets for screening for drug compounds and it was well known that modulation of the level of cAMP or IP3 lead to modulation of neuronal viability. Further, it was well known in the art that the loss of neurons in the substantia nigra is involved in the etiology of Parkinson's disease. Finally, the specification teaches that the novel GPCR sequences can be used for screening for compounds that act as pharmaceutical agents.

Therefore, Applicants assert that a well established, specific, substantial and credible utility for the hARE-2 sequence has been provided and respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn.

Claims 77-106 also stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, on the basis that the claims allegedly lack utility. In light of the arguments above, Applicants respectfully submit that those skilled in the art would recognize both the utility of the invention and how to use it. Moreover, methods of screening for modulators of GPCRs were well known in the art at the priority filing date of the present application, and such methods were described in the earliest priority document. See, for example, Sections D.1. and D.2. on pages 15-17 of Provisional Application 60/136,436, filed on May 28, 1999. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

In conclusion, Applicants respectfully assert that the claimed inventions directed to hARE-2 have a well-established utility, and that the Office Action has not provided any reason for one of ordinary skill in the art to doubt the credibility of such utility. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 101 and § 112, first

paragraph. Further, Applicants assert that the claims are in condition for allowance, and respectfully request notification to that effect.

The Commissioner is hereby authorized to charge any fee or underpayment thereof or credit any overpayment to deposit account no. 50-1275.

Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

Respectfully submitted,
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